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Complete List of Authors:	Vetter, Nora; Universitatsklinikum Carl Gustav Carus, Department of Psychiatry; Universitatsklinikum Carl Gustav Carus, Department of Child and Adolescent Psychiatry Buse, Judith; Universitatsklinikum Carl Gustav Carus, Department of Child and Adolescent Psychiatry Backhausen, Lea; Universitatsklinikum Carl Gustav Carus, Department of Child and Adolescent Psychiatry Rubia, Katya; King's College London, Institute of Psychiatry, Smolka, Michael; Technische Universität Dresden, Department of Psychiatry and Psychotherapy, Section of Systems Neuroscience Roessner, Veit; University Hospital Carl Gustav Carus Dresden, Child and Adolescent Psychiatry
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Anterior insula hyperactivation in ADHD when faced with distracting negative stimuli

Nora C. Vetter[1,2], Judith Buse[2], Lea L. Backhausen[2], Katya Rubia[3], Michael N. Smolka[1*], Veit Roessner[2*]

[1] Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Germany

[2] Department of Child and Adolescent Psychiatry, Faculty of Medicine of the TU Dresden, Germany

[3] Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

[*] The two last authors share senior authorship.

Corresponding author:

Nora C. Vetter

Department of Child and Adolescent Psychiatry

Faculty of Medicine Carl Gustav Carus

Technische Universität Dresden

Fetscherstrasse 74

01307 Dresden, Germany

Tel. +49 (0)351 458-7166

Fax +49 (0)351 458-5754

E-Mail: nora.vetter@tu-dresden.de

http://orcid.org/0000-0003-1477-5395

Abstract

Patients with Attention Deficit Hyperactivity Disorder (ADHD) suffer from poor emotion regulation that might arise from problems in the distribution of attentional resources when confronted with emotional distractors. Previous studies investigating the neurocognitive basis of these problems remain inconclusive. Moreover, most of these studies did not exclude participants with comorbidity, particularly of conduct or oppositional defiant disorder. The aim of this study was to assess alterations in fronto-limbic activation in ADHD adolescents specifically during negative distractors in an emotional attention task. For this purpose we used functional magnetic resonance imaging (fMRI) to assess 25 boys with non-comorbid ADHD and 25 typically developing (TD) boys while they performed an emotional attention task with positive, negative and neutral emotional distractors. Adolescents with ADHD had increased activation relative to TD specifically during the negative valenced stimuli in an emotional processing network comprising left insula reaching into the inferior frontal gyrus. The findings suggest altered salience processing in ADHD of negative valenced emotional stimuli that may lead to higher distractibility in ADHD specifically when faced with negative emotional distractors.

Keywords: fMRI, adolescence, attention, emotion, emotional distractors

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common child and adolescent psychiatric disorders affecting 3 to 9% of children and adolescents [Barkley, 2014]. ADHD is defined by problems with inattention, hyperactivity and impulsiveness [American Psychiatric Association, 1994] and is known to have high comorbidity rates with other psychiatric disorders, in particular oppositional defiant disorder (ODD; 67%) and conduct disorder [CD; 46%, Steinhausen et al., 2006]. Besides psychosocial interventions, psychostimulant medication, i.e. methylphenidate (MPH), is considered the first-line treatment in cases of pure ADHD [Kutcher et al., 2004].

Patients with ADHD also show deficits in executive functions (EF), i.e. cognitive functions responsible for the performance of goal-directed behavior. EF can be divided into "cool" and "hot" EF. "Cool" EF refer to abstract cognitive functions, such as working memory, attention, cognitive flexibility, planning and inhibitory control, that do not involve rewards or emotions [Zelazo and Müller, 2002]. "Cool" EF are typically investigated with tasks like the Wisconsin Card Sorting Test, the Go/No-Go, Color-Word Stroop or the Eriksen Flanker Tasks [Zelazo and Carlson, 2012] and involve lateral inferior and dorsolateral frontostriatal and frontoparietal networks [Krain et al., 2006; Rubia, 2018; Zelazo and Müller, 2002]. "Hot" EF refer to cognitive functions that involve motivationally or emotionally salient decision making and goal setting [Zelazo and Müller, 2002]. There is a conceptual debate on which tasks are part of "hot" EF [Welsh and Peterson, 2014]. Typically, "hot" EF are investigated by delay discounting tasks, gambling tasks, or risky choice tasks [Zelazo and Carlson, 2012] and are mainly subserved by a network spanning the orbital- and ventromedial prefrontal cortex (PFC) and limbic system [Krain et al., 2006; Zelazo and Müller, 2002].

Numerous studies demonstrate behavioral deficits in "cool" EF in patients with ADHD, in particular in attention and inhibitory control [Willcutt et al., 2012]. These deficits have been shown to be associated on the neural level with lateral frontal hypoactivation in ADHD [for a review see Rubia et al., 2014].

Far fewer studies have examined "hot" EF in patients with ADHD and the existing studies reveal mixed results [Shaw et al., 2014]. Among "hot" EF it can be further differentiated between reward-related "hot" EF involving motivation, i.e. reward anticipation and reward processing, and emotion-related "hot" EF, i.e. the ability to focus on a primary task in the presence of distracting emotional stimuli [Zelazo and Müller, 2002]. This ability has been termed emotional attention [Vuilleumier and Huang, 2009].

Behavioral impairments have also been found in reward-based "hot" EF functions as measured in temporal discounting and gambling tasks, with, however, more inconsistent findings [Groen et al., 2013; Noreika et al., 2013; Willcutt et al., 2008]. One of the most consistent functional magnetic resonance imaging (fMRI) findings of reward-based "hot" EF is reduced ventral striatum activation during reward anticipation, as shown in a recent meta-analysis of 8 fMRI studies of a monetary reward anticipation task using region of interest analysis in 340 ADHD patients and healthy controls [Plichta and Scheres, 2014]. Nevertheless, brain abnormalities have also been observed in other typical areas of reward-based decision making during gambling and temporal discounting tasks such as ventromedial prefrontal and orbitofrontal cortex, striatal and limbic regions [Carlisi et al., 2016; Norman et al., 2017; Ortiz et al., 2015; Plichta et al., 2009; Rubia et al., 2009a; Wilbertz et al., 2013].

However, both performance and brain activation abnormalities in reward-related "hot" EF may be more strongly associated with CD and ODD symptoms, which often occur comorbid

to ADHD [Connor et al., 2010; Steinhausen et al., 2006], than with ADHD symptoms themselves [Hobson et al., 2011; Rubia, 2011].

Compared to research on reward-related "hot" EF, research on emotional attention in ADHD is clearly underrepresented [Shaw et al., 2014]. So far, there are only four fMRI studies in adolescents with ADHD that assessed the ability to focus on a primary task, while a distracting emotional stimulus was present, using the emotional Stroop [Hwang et al., 2015a; Passarotti et al., 2010a; Posner et al., 2011a], and the emotional n-back task [Passarotti et al., 2010b]. To our knowledge, only one other fMRI study has tested emotional attention in adults with ADHD [Schulz et al., 2014], using the emotional Go/No-Go task.

Five other fMRI studies on adolescents with ADHD presented emotional stimuli, i.e. faces or stimuli from the International Affective Picture System (IAPS), and asked to rate ones subjective fear [Brotman et al., 2010] / gender [Marsh et al., 2008], respond when viewing a happy face [Malisza et al., 2011] or passively view these stimuli [Herpertz et al., 2008; Posner et al., 2011b.

With regard to the behavioral data, some studies found no difference between adolescents with ADHD and typically developing (TD) adolescents [Brotman et al., 2010; Malisza et al., 2011; Passarotti et al., 2010b], while others report adolescents with ADHD to show greater distraction by the emotional (mostly the negative) stimuli measured by longer reaction times [RT, López-Martín et al., 2013; Passarotti et al., 2010a; Villemonteix et al., 2017] or less accuracy [Posner et al., 2011a]. Some studies showed longer RT independent of the emotional valence [Hwang et al., 2015; Marsh et al., 2008; Van Cauwenberge et al., 2015].

With regard to the fMRI data, hyper- or hypoactivation in ADHD during emotional attention for positive or negative stimuli was found in all four studies on emotional attention in ADHD in the PFC [Hwang et al., 2015; Passarotti et al., 2010a; Passarotti et al., 2010b;

Posner et al., 2011b]. Depending on the study, altered activations in adolescents with ADHD were also found in other regions such as the anterior cingulate cortex (ACC), the striatum, or temporo-parietal regions [Hwang et al., 2015; Passarotti et al., 2010b; Posner et al., 2011b]. Interestingly, results of hypo- or hyperactivation differed depending on the valence of the distracting emotion [positive or negative, Passarotti et al., 2010a; Passarotti et al., 2010b; Posner et al., 2011a]. During passive viewing or evaluating emotional stimuli specifically for negative emotions, amygdala hyperactivation was found in adolescents with pure ADHD [Brotman et al., 2010] and with ADHD and comorbid CD/ODD [Herpertz et al., 2008; Posner et al., 2011b]; but for different results see Malisza et al. [2011]; Marsh et al. [2008] and Herpertz et al. [2008, pure ADHD].

These findings regarding emotional attention were either interpreted as deficient inhibition/regulation of emotions [Passarotti et al., 2010b; Posner et al., 2011b] or a stronger bottom-up processing, i.e. emotional hyperresponsiveness in ADHD [Hwang et al., 2015]. Enhanced functional connectivity between the amygdala and other regions of emotion processing networks such as the lateral PFC [Posner et al., 2011b], or striatal and occipital regions [Hwang et al., 2015] also suggest an emotional hyperresponsiveness in ADHD towards emotional distractors.

Taken together, previous research on emotional attention as part of "hot" EF in adolescents with ADHD is scarce and results are mixed. However, the control of attentional resources when confronted with emotional distractors plays an important role in everyday life of adolescents with ADHD.

Poor "hot" EF in ADHD has been associated with poor emotion regulation [Castellanos et al., 2006]. In ADHD, emotion regulation problems could potentially arise from problems in emotional attention [for a review see Shaw et al., 2014]. Instead of inhibiting their automatic

impulse and keeping their attention on the primary task by ignoring the emotional distractor [Vuilleumier and Huang, 2009], patients with ADHD may easily get distracted and turn their attention towards the emotional distractor.

For example, in a classroom context, adolescents with ADHD may have the impulse to direct attention towards a hostile peer passing by, thereby failing to direct attention on the current essay. It has been shown that these problems may lead to worse academic and work-related performance in adolescents and young adults with ADHD [Shifrin et al., 2010]. Therefore, characterizing emotional attention in ADHD is of high clinical relevance.

The current study was conducted in order to further elucidate this important research question. To this end, we assessed adolescents with ADHD and TD adolescents with a well-classified emotional attention task, that has been shown to yield valid results both on the behavioral and neural level in TD adolescents [Pilhatsch et al., 2014; Vetter et al., 2015]. The task presents a pair of non-emotional abstract pictures and a pair of pictures from one of three emotional categories (negative, positive or neutral). Participants have to report on one pair whether the items are the same or different, while ignoring the other pair. Importantly, the emotion itself is irrelevant for processing the task, it is a distractor in both conditions, either in the attention focus (focal) or spatially outside the attention focus (peripheral). Hence, two experimental conditions were created: “attending emotional stimuli/ignoring abstract stimuli”, with emotional stimuli being focal distractors, and “ignoring emotional stimuli/attending abstract stimuli” with emotional stimuli being peripheral distractors. For both conditions, a longitudinal fMRI study on 144 TD adolescents showed a progressive increase of ACC and bilateral inferior frontal gyrus (IFG) activation between the ages of 14 to 16 years. Also, left anterior insula activation increased for attending positive and ignoring negative stimuli from age 14 to 16 [Vetter et al., 2015]. The amygdala has been shown to be differentially activated

for negative stimuli in 164 fourteen-year-olds with a family history of depression [Pilhatsch et al., 2014].

We included only adolescents with pure ADHD, i.e. without any comorbidity, because 60% of patients with ADHD have a comorbidity with CD/ODD [Connor et al., 2010] and including these patients is an important confound rarely addressed in the neuroimaging literature [Rubia, 2011].

Further, we assessed only boys due to the larger prevalence for males in ADHD [Polanczyk et al., 2007; Willcutt, 2012] and to achieve greater homogeneity across participants given evidence for gender differences in brain activation in ADHD patients [Poissant et al., 2016; Valera et al., 2009].

Aims of the study

Taken together, the current study aimed to investigate the neural processing of attention control in the presence of distracting negative and positive emotional stimuli in adolescents with ADHD compared to TD adolescents, while excluding comorbidity with other psychiatric disorders, in particular CD and ODD.

Based on the previous results on emotional attention we expected adolescents with ADHD to show alterations in brain activation compared to TD adolescents in a) the regions recruited by adolescents in this specific task, namely the IFG, ACC, anterior insula, and amygdala [Pilhatsch et al., 2014; Vetter et al., 2015], and b) in regions of the lateral or medial PFC that have previously shown to be differentially activated in adolescents with ADHD during emotional attention tasks [Hwang et al., 2015; Passarotti et al., 2010a; Passarotti et al., 2010b; Posner et al., 2011a]. Regarding the role of the emotional valence, previous findings of this task show that it elicits stronger distraction for negative than positive stimuli both in

behavioral [slower RT for negative versus neutral, but not positive versus neutral, Pilhatsch et al., 2014; Vetter et al., 2015] and neural findings [Pilhatsch et al., 2014]. Therefore, we focused on trials with negative stimuli and expected to find alterations for adolescents with ADHD versus TD adolescents in these trials on a whole brain basis in the PFC, specifically IFG, ACC, anterior insula, and amygdala.

Given that the amygdala is a small region and was found to be hyperactivated in ADHD during negative emotions [Brotman et al., 2010; Posner et al., 2011b; Wilbertz et al., 2013; Wilbertz et al., 2015], which we hypothesized would also be observed in this study, we in addition conducted a region of interest (ROI) analysis in the amygdala.

Methods

Participants

The study was carried out according to the latest version of the Declaration of Helsinki and approved by the ethics committee of the TU Dresden. Both participants and parents or legal guardians respectively gave their written informed consent. Participants with ADHD were recruited among referrals to the inpatient and outpatient clinics of the Department of Child and Adolescent Psychiatry of the University Hospital Dresden. ADHD was diagnosed according to the ICD-10 [World Health Organization, 1992] by board certified child and adolescents psychiatrists. TD boys were recruited by announcements in the Department of Child and Adolescent Psychiatry and Psychotherapy at the University Hospital Dresden, local schools, doctors' offices and a local parish.

Exclusion criteria were any axis-I disorder comorbid to ADHD or an IQ<80. Participants were screened for (comorbid) psychiatric disorders with the Mini International

Neuropsychiatric Interview for Children and Adolescents [M.I.N.I.-Kid, Sheehan et al., 1998]. The IQ was estimated with a short version of the Wechsler Intelligence Scale for Children [WISC-IV, German adaptation, Petermann and Petermann, 2010].

Initially, we measured each of our in- and outpatients within the age range of 11-17 years, who were diagnosed with ADHD and willing to take part in our study (total of 43 boys with ADHD). At the same time we measured each TD boy within the age range of 11-17 years, who volunteered to take part in the study (total of 37 TD boys). Out of the 43 boys with ADHD, six had to be excluded due to motion artifacts, six due to low behavioral performance during the fMRI task, i.e. more than 30% incorrect answers, and one due to ferromagnetic artifacts and large neuroanatomical abnormalities, respectively. Two TD boys had to be excluded due to motion artifacts, two due to low behavioral performance and two because they did not complete the fMRI session. The remaining sample of 29 boys with ADHD and 31 TD boys were not group-matched in terms of IQ, socioeconomic status or pubertal status. In order to achieve a group-matching, at least with regard to the most important variables (age, pubertal status and IQ), we had to exclude ADHD boys with very low (n = 4) and TD boys with very high IQ (n = 6). This led to a sample of 25 boys with ADHD versus 25 TD boys. The demographics, clinical characteristics and group comparisons of the sample are presented in Table I. The final subsample included in the present analysis is not identical to the subsample in previous structural MRI (sMRI) work due to no task-dependent exclusion criteria in Backhausen et al. [2016, proposing a visual quality control rating system for T1-weighted images to ensure high assessment standards]. None of the (ADHD/TD) participants had mean RT higher than 3 standard deviations (SD) from the mean of the respective (ADHD /TD) samples. Thirteen boys with ADHD were regularly taking MPH (mean duration = 30 ± 41 months), but were taken off methylphenidate (MPH) for at least 48 hours prior to scanning. Five boys with ADHD had taken MPH previously (mean duration = 39 ± 30

months) but stopped one to four years before the study. Seven boys with ADHD had never been pharmacologically treated for ADHD.

Participants completed two visits with 1-4 weeks in between. During the first visit, the WISC-IV and the M.I.N.I.-Kid were assessed. At the second visit, the fMRI assessment took place. First, the fMRI paradigm reported in the present paper was assessed followed by two structural measurements (T1 and diffusion tensor imaging and a second fMRI paradigm [a probabilistic reversal learning (PREL) task, Javadi et al., 2014]. Participants and their parents filled in questionnaires in between these two visits (see Table I). All participants received 30€ plus around 5 – 10€, depending on their performance in the PREL paradigm, as monetary compensation.

Stimuli, design and procedure

Based on previous work [Vuilleumier et al., 2001] we developed a perceptual discrimination task, in which participants decided whether stimuli within a pair of visual target stimuli were the same while another pair of stimuli was presented as distractors. In each trial a pair of non-emotional control pictures and a pair of pictures from one of three emotional categories (negative, positive, neutral) taken from the IAPS was shown. The selection of negative and positive IAPS stimuli was balanced with respect to normed emotional valence and arousal ratings (supplementary Table SI). Positive and negative stimuli did not differ in their arousal levels; $T(98) = .846$, $p = .4$. The arousal levels of both positive ($T(98) = 15{,}483$, $p < .001$) and negative ($T(98) = 16{,}947$, $p < .001$) stimuli differed significantly from neutral ones. Non-emotional control pictures were created by shredding the chosen IAPS pictures beyond recognition using picture manipulation software (www.gimp.org). The luminance was not matched across the three valence conditions.

One pair was arranged horizontally and the other vertically around a fixation cross (see Figure 1). Participants had to attend to the horizontal or vertical pair for a given trial as indicated by a task cue (double-arrow) and report whether the two items of the pair were the same (which was the case in 50%) or different. In half of trials participants had to compare IAPS pictures (attending emotional stimuli, i.e. emotional stimuli as targets) and in the other half abstract shredded pictures (ignoring emotional stimuli, i.e. emotional stimuli as distractors). Temporal positioning of IAPS or shredded pairs was random. Altogether, there were six different trial types: Attending emotional stimuli (negative, positive, neutral) while ignoring abstract stimuli (shredded control stimuli) and ignoring emotional stimuli (negative, positive, neutral) while attending abstract stimuli (shredded control stimuli). The attending emotional stimuli and ignoring emotional stimuli conditions were presented counterbalanced. In total, there were twenty trials per condition, pseudo-randomly interleaved by jittered inter-stimulus intervals.

One trial consisted of the following phases: After a task cue (1s), two picture pairs were shown for 1s on the next screen. During the presentation of the picture screen and the following 1.5s the participant responded via button press (maximum time to answer 2.5s). After the picture screen jittered inter-stimulus intervals were employed (mean: 5000ms, range: 3000 - 7000ms) presenting a fixation cross. The mean trial length was seven seconds with a total of 120 trials. The whole functional run lasted about 14 minutes.

Behavioral data were collected by ResponseGrips (©NordicNeuroLab) with a button on a grip in the right hand. Task presentation and recording of the behavioral responses was performed using Presentation® software (version 11.1, Neurobehavioral Systems, Inc., Albany, CA). The scanning session was preceded by a practice session inside the scanner using stimuli not included in the experiment.

Analysis of behavioral data

Statistical analyses were performed using SPSS for Windows (Version 25) on the mean RT and valid trials. Repeated measures ANOVAs with a 2 x 2 x 3 factorial design were calculated using a threshold of $p < .05$ with the between-subject factor group (ADHD, TD), and the within-subject factors attention (attending emotional stimuli, ignoring emotional stimuli), and emotional valence (negative, positive, neutral).

Functional imaging

Image acquisition. Scanning was performed with a 3T whole-body MRI scanner (Magnetom TRIO, Siemens, Erlangen, Germany) equipped with a 12-channel head coil. For functional imaging, a standard Echo Planar Imaging (EPI) Sequence was used (repetition time, TR: 2410ms; echo time, TE: 25ms; flip angle: 80°). FMRI scans were obtained from 42 transversal slices, tilted up 30° clockwise from the anterior commissure–posterior commissure line to improve signal in the orbitofrontal cortex and minimize susceptibility artifacts. A thickness of 2mm (1mm gap), a field of view (FOV) of 192 x 192mm and an in-plane resolution of 64 x 64 pixels resulted in a voxel size of 3 x 3 x 3mm. Only marginal sections of the most superior part of the parietal cortex and the most inferior part of the cerebellum were omitted. Moreover, a 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image data set was acquired (TR = 1900ms, TE = 2.26ms, FOV = 256 x 256mm, 176 slices, 1 x 1 x 1mm voxel size, flip angle = 9°). Images were presented via a head-coil-mounted display system based on LCD technology (NordicNeuroLab AS, Bergen, Norway).

Analysis of fMRI data

Preprocessing. Functional images were preprocessed and statistically analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). For each participant, functional images were first slice-time corrected by using the middle slice as reference, then realigned to the first image by 6-degree rigid spatial transformation, spatially normalized to the standard space defined by the Montreal Neurological Institute (MNI) EPI template and smoothed with a Gaussian kernel of 8mm at full-width half maximum. Maximum participant movement at each time point in any direction did not exceed 3.5mm or degrees.

Statistical analysis. In the first-level analysis, a fixed effects analysis was computed for each participant on the basis of the general linear model within each voxel of the whole brain by modeling the different conditions (emotional valence and attention) as regressors of interest. Six regressors of interest, attending (1) negative, (2) positive, and (3) neutral emotional stimuli, as well as ignoring (4) negative, (5) positive, and (6) neutral emotional stimuli were modeled at the point of presentation as stick functions convolved with a canonical hemodynamic response function. Additionally, trials with missing or wrong responses were modeled as a separate regressor, i.e. only correct answers were analyzed. The six subject-specific movement regressors, which were derived from the rigid-body realignment, were included as covariates of no interest. Each component of the model served as a regressor in a multiple regression analysis. A high-pass filter with cut-off 128s was applied to remove the low frequency physiological noise [Henson, 2006]. Also, an AR(1) model was employed for the residual temporal autocorrelation [Henson, 2006]. We always used the neutral condition as the reference category to eliminate neural processes not related to emotional valence. Four contrasts of interest were thus computed within each subject: attending negative minus attending neutral stimuli (contrast 1), ignoring negative minus

ignoring neutral stimuli (contrast 2), attending positive minus attending neutral stimuli (contrast 3) and ignoring positive minus ignoring neutral stimuli (contrast 4). The first-level contrast images from the weighted beta-images were introduced into a second-level whole brain random-effects analysis to allow for population inference.

Whole brain analysis of group differences. At the group level, an ANOVA was computed using a 2 x 2 x 2 full factorial model with the between-subject factor group (ADHD, TD) and the within-subject factors attention (attending emotional stimuli, ignoring emotional stimuli) and emotional valence (negative, positive) using contrasts 1, 2, 3, and 4. Aiming at an overall picture of group differences, we analyzed them on a whole brain level. The resulting set of significant voxel values constituted a SPM map. For significant clusters we created masks and applied them to extract percent signal change from the whole cluster with rfxplot [Glaescher, 2009]. All brain coordinates are reported in MNI atlas space at a voxel level of $p < .001$ with a cluster level threshold of $p < .05$. The size of the ROIs did not vary between participants.

Region of interest analysis of the amygdala. The left and right amygdala each were used as an anatomical ROI generated with the WFU-pickatlas using the Talairach Daemon Brodmann atlas. Percent signal change of these anatomical ROIs was extracted from the whole ROI with rfxplot. For the left and the right amygdala, a separate ANOVA was computed using a 2 x 2 x 2 full factorial model in SPSS for Windows (Version 25) with the between-subject-factor group (ADHD, TD) and the within-subject-factors attention (attending emotional stimuli, ignoring emotional stimuli) and emotional valence (negative, positive).

Results

Behavioral results

Reaction times. For RT as the dependent variable, the ANOVA revealed no main effect of group, $F(1,48) = 2.23$, $p = .142$, *partial* $\eta^2 = .044$. There was a main effect of attention, $F(1,48) = 10.34$, $p = .002$, *partial* $\eta^2 = .177$, driven by faster RT for attending than ignoring emotional stimuli. The main effect of valence showed a trend, $F(2,96) = 2.61$, $p = .079$, *partial* $\eta^2 = .052$, i.e. lowest RT for neutral followed by positive and negative emotion. The only significant interaction emerged for attention x valence, $F(2,96) = 13.1$, $p < .001$, *partial* $\eta^2 = .214$, driven by slower RT for attending negative compared to neutral emotional stimuli, $t(50) = 4.92$, $p < .001$, $d = .378$, and for attending negative compared to positive emotional stimuli $t(50) = -3.79$, $p < .001$, $d = .33$, while RT for ignoring emotional stimuli did not differ between the valences, *p's* > .205. The pattern of results for RT for each condition was similar in the ADHD and the TD group (see Figure 2).

Valid trials. All correct trials were considered as valid trials (misses or incorrect responses were excluded). For valid trials as the dependent variable, the ANOVA revealed a main effect of group, $F(1,48) = 10.14$, $p = .003$, *partial* $\eta^2 = .174$, driven by fewer valid trials for the ADHD group than the TD group. The ANOVA revealed a main effect of attention, $F(1,48) = 30.13$, $p < .001$, *partial* $\eta^2 = .386$, driven by more valid trials for attending compared to ignoring emotional stimuli. There was no main effect of valence, $F(2,96) = .27$, $p = .76$, *partial* $\eta^2 = .006$, but a significant attention x valence interaction, $F(2,96) = 3.22$, $p = .044$, *partial* $\eta^2 = .063$, driven by fewer valid trials for attending negative versus neutral emotional stimuli, $t(50) = -2.41$, $p = .02$, $d = .289$, while the number of valid trials for ignoring emotional stimuli did not differ between the valences, *p's* > .185. The interactions of group x attention, group by valence, and group by attention by valence were not significant, *p's* >

.187. See Table II for number of valid trials and percentage correct as well as group comparisons for each condition. The range and mean of valid trials per person per condition that entered the first-level GLM are presented in supplementary material SII.

As a plausibility check, RT and valid trials for the TD group were in the range as recently reported in a similar sample [Vetter et al., 2015].

As valid trials did not consistently meet assumptions of parametric statistics (normality and homogeneity of variances), results of nonparametrical analyses (Mann-Whitney U test) are provided in supplementary materials SIII. These analyses did not differ appreciably from the reported findings on valid trials.

fMRI results

Whole brain analysis

Main effects of attention and emotional valence as a proof of concept.

First, to reassure that the paradigm elicited activations in the regions previously found for emotional attention [Corbetta et al., 2008; Corbetta and Shulman, 2002; Vuilleumier and Huang, 2009], the main effects of attention and emotional valence were analyzed in the whole group. Therefore, a 2 x 2 x 2 ANOVA with the within-subject factors group (ADHD, TD), attention (attending emotional stimuli, ignoring emotional stimuli) and emotional valence (negative, positive) was analyzed. Overall, regions overlap with those found in Vetter et al. [2015] and Pilhatsch et al. [2014] using the same paradigm in TD adolescents. Results showed higher activity in the left IFG (x, y, z = -51, 27, 12; k = 87, t = 4.86, cluster-level p = .01) and left middle temporal gyrus (x, y, z = -60, -57, 21; k = 103, t = 4.26, cluster-level p =

.006) for attending versus ignoring emotional stimuli. No significant clusters emerged for ignoring versus attending emotional stimuli.

For trials containing negative stimuli in contrast to trials containing positive stimuli the activity was higher in the left amygdala extending to the hippocampus, (x, y, z = -33, 3, -27; k = 72, t = 4.21, cluster-level p = .017). No significant clusters emerged for positive versus negative stimuli.

Overall, for the main effects of attention and valence results were similar when analyzing both groups (ADHD, TD) separately (see supplement SIV).

Group effects.

The main effect of group was not significant neither for ADHD>TD nor TD>ADHD participants. To capture all possible group effects the two-way interactions group x emotional valence and group x attention were analyzed but yielded no significant results.

Further, we tested for the simple main effect of group in trials containing negative stimuli. We choose this approach since only negative (versus positive) stimuli elicited significant brain activation but not vice versa (see main effect of valence) and given the slower RT for negative versus neutral but not positive versus neutral stimuli. Therefore, we hypothesized that negative stimuli would elicit a stronger distraction effect.

For negative stimuli, significant activation resulted for ADHD>TD in the left anterior insula, bordering the IFG (x, y, z = -45, 18, -6; k = 192, t = 4.31, cluster-level p < .001), the right anterior insula, bordering the IFG (x, y, z = 51, 18, -6; k = 121, t = 3.69, cluster-level p = .003), the left precentral gyrus (x, y, z = -33, -15, 57; k = 80, t = 4.18, cluster-level p = .013), the right medial superior frontal gyrus bordering the midcingulate cortex (x, y, z = 3, 27, 45; k = 49, t = 3.95, cluster-level p = .043), and the right supplementary motor area (SMA; x, y, z = 3, -21, 54; k = 87, t = 3.65, cluster-level p = .01). No significant activation for negative

stimuli emerged for TD>ADHD participants. For positive stimuli, there was no significant activation for ADHD>TD or TD>ADHD. The cluster of the left anterior insula bordering the IFG is shown in Figure 3.

As described in the methods section we reported all clusters surviving a $p < .05$ correction on the cluster level with a preselection threshold on the voxel-level of $p < .001$. We mainly used this cluster level threshold of $p < .05$ in order to enable comparability with results of previous publications. However, according to Eklund et al. [2016] this cluster level threshold might lead to too many false positives. On the other hand, a family-wise-error correction preselection threshold might be too conservative. A cluster level threshold of $p < .001$ can be considered a reasonable trade-off. When applying the cluster-level threshold of $p < .001$ the only surviving cluster is the left anterior insula, bordering the IFG (x, y, z = -45, 18, -6; k = 192, $t = 4.31$, cluster-level $p < .001$). Therefore, we focused on this cluster as the main result in the discussion.

Amygdala ROI analysis

For percent signal change in the left anatomical amygdala ROI no main effect of group, $F(1,48) = 0.512$, $p = .478$, partial $\eta^2 = .011$, or of attention was found, $F(1,48) = 1.487$, $p = .229$, partial $\eta^2 = .03$. There was a significant main effect for emotional valence, $F(1,48) = 10.47$, $p = .002$, partial $\eta^2 = .179$, i.e. the left amygdala was activated more strongly for negative versus positive stimuli. The only significant interaction was for group x valence, $F(1,48) = 7.21$, $p = .01$, partial $\eta^2 = .131$. Post hoc t-tests showed that this was driven by ADHD adolescents showing a higher left amygdala activation for negative versus positive stimuli, $t(24) = -3.93$, $p = .001$, while TD adolescents showed no difference in left amygdala activation for negative and positive stimuli, $t(24) = .68$, $p = .679$ (see Figure 4).

For the right amygdala, analysis of percent signal change indicated no main effect of group, $F(1,48) = 2.53$, $p = .118$, partial $\eta^2 = .05$, but a main effect for emotional valence, $F(1,48) = 11.29$, $p = .002$, partial $\eta^2 = .19$, and a main effect for attention, $F(1,48) = 4.87$, $p = .032$, partial $\eta^2 = .092$, i.e. the right amygdala was activated more strongly for negative than positive stimuli as well as for attending than ignoring emotional stimuli. The interactions were not significant, p's $> .379$.

Additional exploratory analyses

Exploratory analysis of valid trials and neural activation.

Given the significant group differences in total valid trials and neural activation for negative stimuli, correlations for the ADHD and the TD group separately were calculated between total valid trials and percent signal change in the left anterior insula found in the whole brain analyses and the ROI of the left amygdala. For the ADHD group, percent signal change of the left amygdala for negative stimuli correlated significantly negatively with total valid trials, $r = -.5$, $p = .012$ (see Figure 5), while the percent signal change of the left insula did not correlate with total valid trials, $p > .58$. For the TD group, percent signal change for negative stimuli in left amygdala/ insula did not correlate with total valid trials, $p > .19$.

When including valid trials as a covariate in the whole brain fMRI analyses and the ROI-based amygdala analyses effects and clusters remain mostly the same except for the effects in the right amygdala, which do not show significance anymore.

Covariate analysis.

To control for potential confounders, we included IQ, socioeconomic status (Winkler index including parents' school education, professional education, recent professional status and family income), and state as well as trait anxiety (STAI-S; STAI-T) as covariates in the whole brain fMRI analyses and the ROI-based amygdala analyses. Overall, the results did not change (see supplementary material SV).

Analysis of original sample without matching.

Overall, fMRI results did not change when we analyzed the original sample before matching (31 TD vs. 29 ADHD; see supplementary material SV).

MPH subgroup analysis.

In addition, we did an exploratory analysis comparing ADHD subgroups based on stimulant medication use (group 1: n=7 MPH naïve lifetime; group 2: n=5 previous long-term MPH medication years before the study; group 3: n=13 current long-term MPH medication at time of study paused 48h before MRI scan) and the TD group (see supplementary material SVI for methods and detailed results).

Behaviorally, patients who were MPH naïve throughout their lifetime had fewer total valid trials in comparison to TD while subgroups with previous and current long-term MPH use did not differ in total valid trials from the TD group. There were no differences in RT between the four groups.

Neurally, we compared percent signal changes from (1) the left insula/IFG cluster (that resulted from a higher percent signal change for ADHD>TD for negative stimuli) and (2) the left amygdala ROI in the three ADHD groups and the TD group. In the left insula/IFG all three ADHD groups had higher percent signal change compared to the TD group (main effect

of group). An interaction of group x valence was driven by previous long-term MPH having higher left insula/IFG activation than TD for negative but not for positive stimuli.

For the left amygdala an interaction of group x valence was driven by adolescents with previous long-term MPH medication showing higher activation for negative versus positive stimuli in contrast to the other groups who showed no differences between the valences.

Discussion

This study investigated emotional attention in boys with ADHD and TD boys using a task that included neutral, negative and positive emotional stimuli and hence was aimed to test for emotion-specific neurofunctional differences between ADHD and TD. Furthermore, while some previous fMRI studies of emotional attention processing included adolescents with CD/ODD, we included only boys with ADHD without any comorbidity.

Behaviorally, boys with ADHD showed similar RT while showing more errors, i.e. fewer valid trials, than TD boys. Neurally, in line with our hypothesis, we found that boys with ADHD relative to TD boys had increased activation in a region of the PFC, namely the left IFG for negative emotional stimuli. This activation extended into the left anterior insula. The amygdala ROI analysis revealed that boys with ADHD compared to TD boys had increased activation for negative stimuli in the left amygdala. Also, the left amygdala (hyper-) activation in ADHD correlated negatively with the number of valid trials, suggesting that the amygdala hyperfunction was associated with poorer task performance. As effects mostly remain when including valid trials as a covariate, it is unlikely that findings on a neural level were produced exclusively by behavioral differences.

The behavioral results show overall differences between ADHD and TD in valid trials independent of specific negative or positive emotional valence. The results add to the yet

sparse literature of emotional attention in ADHD and are in line with previous work [Hwang et al., 2015; Marsh et al., 2008; Van Cauwenberge et al., 2015] but differ from findings of emotional interference effects, i.e. differences between ADHD and TD specifically for positive and negative emotional, but not neutral stimuli. One possible reason might be that not only the positive and negative emotional, but also our complex neutral stimuli might have distracted from the task at hand. Behaviorally, more studies are needed that reveal the specific context when a positive or negative emotional or neutral stimulus leads to distraction in ADHD.

Our neural results of amygdala and insula/IFG hyperactivation suggest that adolescents with ADHD have an enhanced response to task-irrelevant negative emotional stimuli, which could reflect increased distractibility (it needs to be kept in mind that the emotion itself is irrelevant for processing the task, it is a distractor in both conditions, either in the attention focus (focal distractor), i.e. attending emotional stimuli, or spatially outside the attention focus (peripheral distractor), i.e. ignoring emotional stimuli). The left amygdala hyperactivation was furthermore associated with worse performance in the task, which would corroborate the hypothesis that the amygdala hyperactivation was an indication of increased distraction leading to worse task performance. The increased distractibility for emotional stimuli could be related to higher bottom-up amygdala activation.

Most previous emotional attention studies except the one by Passarotti et al. [2010a] in adolescents with ADHD did not find IFG/insula hyperactivation for negative emotional stimuli [Hwang et al., 2015; Posner et al., 2011a; Passarotti et al., 2010b], possibly due to the higher cognitive load and/or due to the CD/ODD comorbidity in these studies.

Previous emotional attention tasks had a higher cognitive load [employing e.g. a counting, Hwang et al., 2015; or memory-task (n-back), Passarotti et al., 2010b] compared to our study,

in which participants just had to match pictures. With a higher cognitive load, the task's main effect might be more cognitive rather than emotional. Therefore, the cognitive load in some previous studies could have washed out the effect of the emotional stimuli and partly led to hypo- instead of hyperactivation in the PFC for emotional stimuli [e.g. Posner et al., 2011a] comparable to findings of PFC hypoactivation for "cool" EF in ADHD [Rubia et al., 2014; Rubia, 2018]. Similar results as in our study, namely an IFG hyperactivation for negative emotional stimuli were found by Passarotti et al. [2010a], who also had a low cognitive load (matching color). The increased left amygdala activation in ADHD compared to TD for negative stimuli in our study is also a suggestion that the emotional valence had a stronger effect on neural activation than the cognitive task itself of matching pictures.

Previous emotional attention studies did not find amygdala hyperactivation during negative emotions in ADHD [Hwang et al., 2015; Passarotti et al., 2010b; Passarotti et al., 2010a; Posner et al., 2011a]. However, when integrating our result into emotional studies with passive viewing/evaluating emotion, they are in line with amygdala hyperactivation findings in Brotman et al. [2010], Posner et al. [2011b] and Herpertz et al. [2008, for CD with comorbid ADHD]. In contrast, amygdala hypoactivation [Sterzer et al., 2005] or no amygdala activation differences were found in other studies of passive viewing/evaluating emotion [Herpertz et al., 2008, for pure ADHD; Malisza et al., 2011; Marsh et al., 2008]. Divergent findings could be due to differences between studies in the induced emotions or in the groups of ADHD adolescents either with or without CD/ODD comorbidity.

Due to the highly frightening scenes i.e. depicting violence, wounded or dead people, fear/avoidance is most likely the induced emotion in our study as well as in the paradigms used by Herpertz et al. [2008] who also presented highly frightening IAPS pictures, Brotman

et al. [2010], who provoked attention towards one's own fear and Posner et al. [2011b], who let participants passively view fearful faces.

In contrast, Malisza et al. [2011] showed angry faces and Marsh et al. [2008] let participants rate the gender of fearful faces, which might have induced different emotions or distracted from the induced emotion.

Interestingly, in an adult ADHD study, left insula hyperactivation was also found during presentation of the conditioned stimulus compared to control stimuli in a verbally instructed fear paradigm when correcting for state and trait anxiety influences [Maier et al., 2014].

Most previous studies assessing emotional attention [Brotman et al., 2010; Herpertz et al., 2008; Hwang et al., 2015; Posner et al., 2011a; Posner et al., 2011b; Sterzer et al., 2005] and passively viewing or evaluating emotions [Herpertz et al., 2008; Posner et al., 2011b; Sterzer et al., 2005] also (partly) included adolescents with ODD/CD comorbidity and therefore differentiation between the effects of ADHD or ODD/CD symptomatology is not possible. For example, the amygdala hypoactivation found by [Sterzer et al., 2005] could speculatively be due to ADHD participants with CD, who might not have processed the negative emotional content that much, possibly due to CD-related deficits in emotional empathy, especially with callous-unemotional traits [Cohen and Strayer, 1996; Schwenck et al., 2012]. We demonstrate here that hyperactivation of insula/IFG and amygdala for negative stimuli is present in boys with ADHD without comorbidity with CD/ODD.

The anterior insula has been shown to be smaller in patients with ADHD [Lopez-Larson et al., 2012; Norman et al., 2016]. Furthermore, in a recent large meta-analysis of sMRI and fMRI studies in ADHD children and adults, the anterior insula was the only region with both structural and functional abnormalities [Norman et al., 2016]. The anterior insula has been associated with emotion processing, specifically interoception [Craig, 2009] and has been

suggested to recruit top-down control regions such as the ACC, if necessary [Menon and Uddin, 2010]. In addition, the insula is also a key hub region of the "ventral attention' [Carretié, 2014; Corbetta and Shulman, 2002; Eckert et al., 2009] and "salience' networks [Barrett and Satpute, 2013; Seeley et al., 2007] that enables reorienting to salient environmental stimuli. The amygdala also belongs to these networks; more specifically it is included in a preattentional evaluation network that modulates attentional resources at an early subcortical stage [Carretié, 2014] and therefore also signals the salience of the emotional stimuli. There is consistent evidence from large ADHD samples for an increased functional connectivity and a maturational lag in connectivity of the ventral attention network - especially of the anterior insula - with the default mode network [Sripada et al., 2014b; Sripada et al., 2014a], presumably due to the need to scan for salience in an environment that seems more boring. This insula dysfunction has been interpreted to probably produce excessive distractibility by task-irrelevant stimuli [Sripada et al., 2014b; Sripada et al., 2014a]. However, interestingly, key components of the salience network are underactivated in ADHD during salient cognitive stimuli in tasks of error processing or cognitive control [Cubillo et al., 2011; Cubillo et al., 2012; Norman et al., 2016; Rubia et al., 2007; Rubia et al., 2009b; Rubia et al., 2011b; Rubia et al., 2011a]. The current findings of hyperactivation of the insula during negative stimuli add to the evidence for an insula dysfunction in ADHD, but suggest that the sign of the activation deficit is context-dependent: the insula appears to be underactive in ADHD in the context of cognitive tasks that are typically more boring to these adolescents and hence subjectively "undersalient" [Cubillo et al., 2011; Rubia et al., 2007; Rubia et al., 2009b; Rubia et al., 2011a], while during negative emotions, which are strongly salient for ADHD, the insula seems to be hyperactive. Current findings fit to a recent ADHD sMRI study with a large population-based sample [Albaugh et al., 2017] which found that dimensional, multi-informant measures of ADHD symptomatology in adolescents and RT

variability were negatively associated with ventromedial PFC volume, an area that regulates amygdala activity [Motzkin et al., 2015].

This hyperactivity towards negative stimuli in ADHD - probably related with a heightened affective feeling - can also be termed hyperresponsiveness towards negative stimuli [in line with López-Martín et al., 2013; Passarotti et al., 2010b; Wilbertz et al., 2015]. Speculatively, Wilbertz et al. [2015] suggested that this hyperresponsiveness in ADHD may be the result of a learning history that is biased towards negative events or outcomes, i.e. patients with ADHD may have experienced several emotional negative situations and therefore may be more sensitive towards negative emotions. The emotional hyperresponsiveness has also been suggested to be related to ADHD symptoms of an unusually strong emotional response towards emotional stimuli ["emotional lability', Posner et al., 2011a; Sonuga-Barke et al., 1992], suggesting that the anterior insula and amygdala hyperactivation may underlie this emotional lability.

Regarding medication effects in our study, only patients who were MPH naïve throughout their lifetime performed worse than TD. This could potentially indicate that (current or previous long-term) MPH treatment may normalize performance in emotional attention tasks. This is a finding similar to Posner et al. [2011a] who demonstrated - for negative stimuli - even better performance for ADHD patients under current long-term MPH compared to TD.

Each of our MPH subgroups showed higher activation than TD in the left insula/IFG, indicating no long-term medication effect for MPH intake paused at least 48h before the study. This finding is in line with studies showing that ADHD adolescents with long-term MPH medication (with 48h break before the study) also differed from TD in their brain activation (medial PFC hypoactivation for negative stimuli in Posner et al. [2011a] or amygdala hyperactivation in Posner et al. [2011b]). Speculatively, only the acute

pharmaceutical effect of MPH may lead to a "normalized" brain activation for emotional attention, i.e. no differences from TD as shown for the group with long-term medication without MPH pause in Posner et al. [2011a,b]. However, contrasting findings exist for a "cool" attentional reorienting task showing "normalized" brain activation for the insula and striatum after one year of MPH and one week break before the study [Konrad et al. 2007].

Only one of our subgroups (previous long-term MPH-treated patients) differed between the valences showing higher activation for negative stimuli in the left insula/IFG, and amygdala. However, this group is quite small, so interpretation is difficult.

In general, our MPH-related results have to be treated with caution since the MPH groups were only investigated post hoc and the sample sizes of the MPH subgroups were very small. Future studies with an a priori approach and bigger sample sizes are needed that systematically assess differences in brain activation between adolescents with and without stimulant medication in order to disentangle current or previous long-term medication and short-term discontinuation.

Overall, current findings warrant replication using larger sample sizes. However, our study is sufficiently powered for fMRI studies, where a minimum of 20 subjects has been recommended [Thirion et al., 2007] and well in the common range for ADHD fMRI studies. It is also the largest fMRI study that included "pure" adolescents with ADHD without any comorbidity.

Another limitation relates to the low trial numbers per condition [Murphy and Garavan, 2004]. The lack of findings in the three-way interactions in the fMRI data could be due to low statistical power to detect differences [Button et al., 2013].

It also needs to be pointed out that valence and arousal influences cannot be disentangled because we subtracted neutral from the negative/positive activation in order to eliminate neural processes not related to emotional valence.

Furthermore, the different amount of total valid trials which entered the fMRI analyses for the ADHD and TD groups needs to be considered as a possible confound. Still, as valid trials in the negative stimuli conditions did not differ significantly between the groups this is highly unlikely for our specific findings.

It has been shown that ADHD adolescents have lower IQ and sociodemographical variables [Gaub and Carlson, 1997; Kuntsi et al., 2004; Willcutt et al., 2008], therefore an ideal matching in terms of these variables could not be achieved. However, we controlled for the influence of these variables in covariate analyses and findings remained identical suggesting that these variables did not unduly influence the findings.

Given previous findings of differences in the activation of adolescents with ADHD relative to TD during processing of emotional distractors with and without comorbid ODD/CD [Hwang et al., 2015; Passarotti et al., 2010a; Passarotti et al., 2010b; Posner et al., 2011a], future studies could additionally disentangle the specificity of emotional processing of comorbid ADHD with ODD/CD, pure ADHD, and pure ODD/CD.

This study assessed boys only. Our aim was to achieve greater homogeneity across participants. Thus, we decided to assess boys because ADHD is most prevalent in boys [Polanczyk et al., 2007; Willcutt, 2012] and because there is evidence for gender differences in brain activation [Poissant et al., 2016; Valera et al., 2009]. Previous studies mirror this prevalence in their gender distributions assessing mostly boys [Brotman et al., 2010; Hwang et al., 2015; Marsh et al., 2008; Passarotti et al., 2010b; Posner et al., 2011b; Posner et al.,

2011a]. Nevertheless, future studies are warranted that assess girls and investigate gender-specific differences.

Further, future studies could investigate possible differences in fixation or saccade patterns across conditions. Although we did track eye movement data, due to technical problems there were too few participants to investigate this issue.

In conclusion, this fMRI study of an emotional attention task shows that boys with non-comorbid ADHD relative to TD boys have enhanced activation during negative emotional stimuli in an IFG-insular-limbic emotion and saliency network. The findings suggest that adolescents with ADHD show enhanced neurocognitive saliency processing of negative emotional stimuli which may be associated with enhanced distractibility during negative emotions in ADHD.

The current findings could potentially indicate a heightened emotional responsiveness and possibly unusually strong emotional response towards negative emotional stimuli and may therefore have therapeutic implications. It may be relevant for ADHD patients to know that they easily get distracted by negative emotional stimuli and hence might have problems to control their behavior in the context of negative emotions. Transferred to psychotherapy, ADHD patients might particularly benefit from therapeutic approaches of emotion regulation. In academic contexts, it may be important to try to shield them from negative emotion-eliciting situations in order to focus on the task at hand.

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Table I: Demographics, clinical characteristics and group comparisons (n = 50).

Parameter		ADHD (N=25)	TD (N=25)	Group comparison		
		M (SD)	M (SD)	t	df	P
	Age in years	14.26 (1.88), range 11.29-17.89	14.02 (1.73), range 11.15-16.88	.46	48	.649
	No. of right handers	25	22, 3 bimanual			
	Socioeconomic status[a]	13.51 (4.56)	15.3 (3.73)	-1.49	46	.144
	IQ[b]	106 (9), range 93-120	110 (9), range 92-121	-1.56	48	.126
	Pubertal status[c]	2.84 (0.94), i.e. mid pubertal	2.68 (1), i.e. mid pubertal	.57	48	.569
	State anxiety[d]	38.58 (7.77)	33.72 (4.25)	2.73	47	.009
	Trait anxiety[d]	34.04 (8.14)	31.28 (4.97)	1.44	47	.157
CBCL[e]	Internalizing	60.42 (10.27)	53.25 (9.9)	2.46	46	.018
	Externalizing	59.96 (9.18)	50.67 (9.07)	3.53	46	.001
	Attention	66.63 (7.95)	53.71 (5.38)	6.59	46	< .001
	total	62.92 (8.26)	51.08 (9.72)	4.55	46	< .001
FBB-ADHD[f]	Attention	7.42 (1.1)	4.63 (2)	6	46	< .001
	Hyperactivity	5.92 (2.54)	3.38 (2.75)	3.33	46	.002
	Impulsivity	6 (2.74)	4.08 (2.8)	2.4	46	.02

	total	7.21 (1.29)	4.75 (1.68)	5.7	46	< .001
SBB-ADHD[f]	Attention	6.33 (1.81)	4.76 (1.42)	3.39	47	.001
	Hyperactivity	5.75 (2.33)	4.32 (1.8)	2.41	47	.02
	Impulsivity	5.33 (2.78)	4.8 (2.1)	.76	47	.451
	total	6.08 (1.82)	4.56 (1.45)	3.23	47	.002

[a] Calculation of socioeconomic status included parents' school education, professional education, recent professional status and family income following the procedure suggested by Winkler and Stolzenberg [2009]. Scores for mothers and fathers were averaged into a family-based measure of socioeconomic background. The score ranges from 3 to 21 with higher values indicating higher socioeconomic status.

[b] To estimate general cognitive ability the subtests Vocabulary, Letter-Number Sequencing, Matrix Reasoning, and Symbol Search from the Wechsler Intelligence Scale For Children [WISC-IV, German adaptation; Petermann and Petermann, 2010] were used.

[c] Pubertal status ranges from 1 for prepubertal to 5 for postpubertal status, measured with the Pubertal Development Scale [Petersen et al., 1988] .

[d] State and Trait anxiety were measured with the State Trait anxiety Inventory [Spielberger, 1983]. The anxiety scores in both groups were below clinical significance.

[e] CBCL – Child Behavior Checklist [Achenbach, 1991].

[f] Parent- (FBB) and self-rated (SBB) ADHD scale of the comprehensive diagnostic system for mental disorders in childhood and adolescence [DISYPS II; Döpfner et al., 2008].

Please note that due to assessment difficulties some values are missing for a few participants (n range from 48 of 50 to 50 of 50).

Table II: Number of valid trials and percentage correct (20 trials per condition), group comparisons as parametric tests.

	ADHD (N=25)		TD (N=25)		Group comparison			
	M	SD	M	SD	t	df	P	d
negative targets	17.28 (86.4%)	2.19	18.2 (91.0%)	1.53	-1.723	48	.091	.5
positive targets	17.46 (87.3%)	1.96	18.52 (92.6%)	1.36	-2.265	48	.028	.65
neutral targets	17.64 (88.2%)	1.89	18.88 (94.4%)	1.17	-2.791	48	.008	.81
negative distractors	16.72 (83.6%)	2.28	17.64 (88.2%)	1.41	-1.714	48	.093	.5
positive distractors	16.64 (83.2%)	2.4	17.84 (89.2%)	1.55	-2.104	48	.041	.6
neutral distractors	15.72 (78.6%)	2.73	17.8 (89.0%)	1.66	-3.255	48	.002	.95

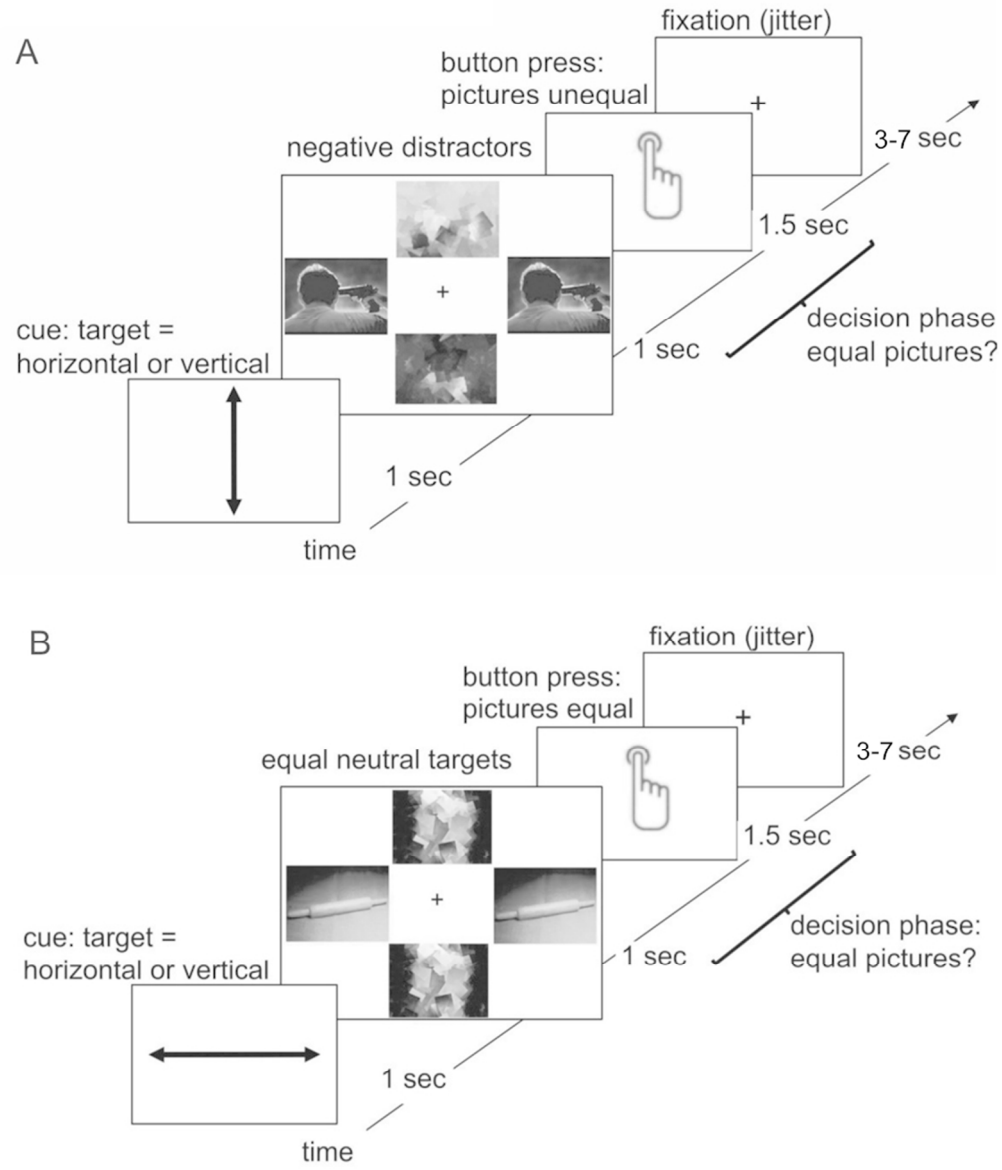

Figure 1: a) Example trial for ignoring emotional stimuli. b) Example trial for attending emotional stimuli.

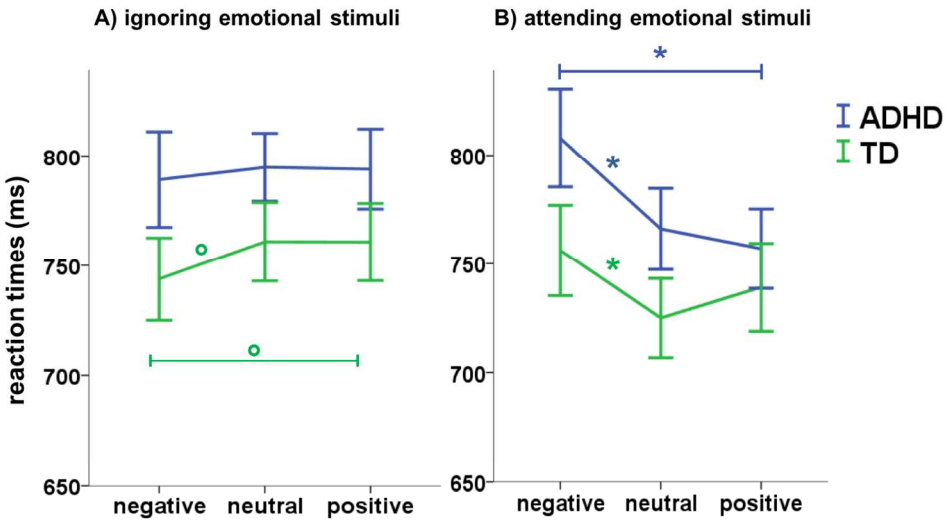

Figure 2: Mean reaction times for A) ignoring emotional stimuli and B) attending emotional stimuli. * p < .05, ° p < .1. Error bars denote SEM. TD= typically developing group, ADHD = Attention Deficit Hyperactivity Disorder group.

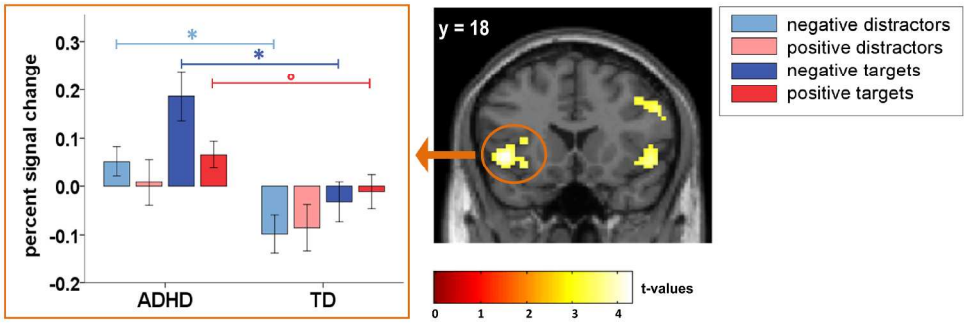

Figure 3: Brain activity associated with the effect of group for negative stimuli only (ADHD > TD) thresholded at $p < .05$ corrected cluster level, $p < .001$ uncorrected at the voxel level. Only the cluster of the left anterior insula, bordering the inferior frontal gyrus survived a cluster level threshold of $p < .001$. Using the mask of this cluster, we further extracted percent signal change. Error bars denote SEM. * $p < .05$, ° $p < .1$. TD= typically developing group, ADHD = Attention Deficit Hyperactivity Disorder group.

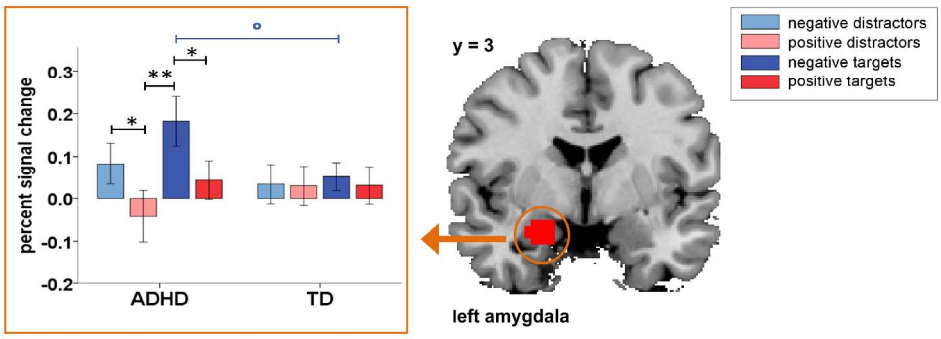

Figure 4: Percent signal change for the left amygdala ROI. We performed within-group comparisons that were significant only for the ADHD group. Error bars denote SEM. ** p < .01; * p < .05, ° p < .1. TD= typically developing group, ADHD = Attention Deficit Hyperactivity Disorder group.

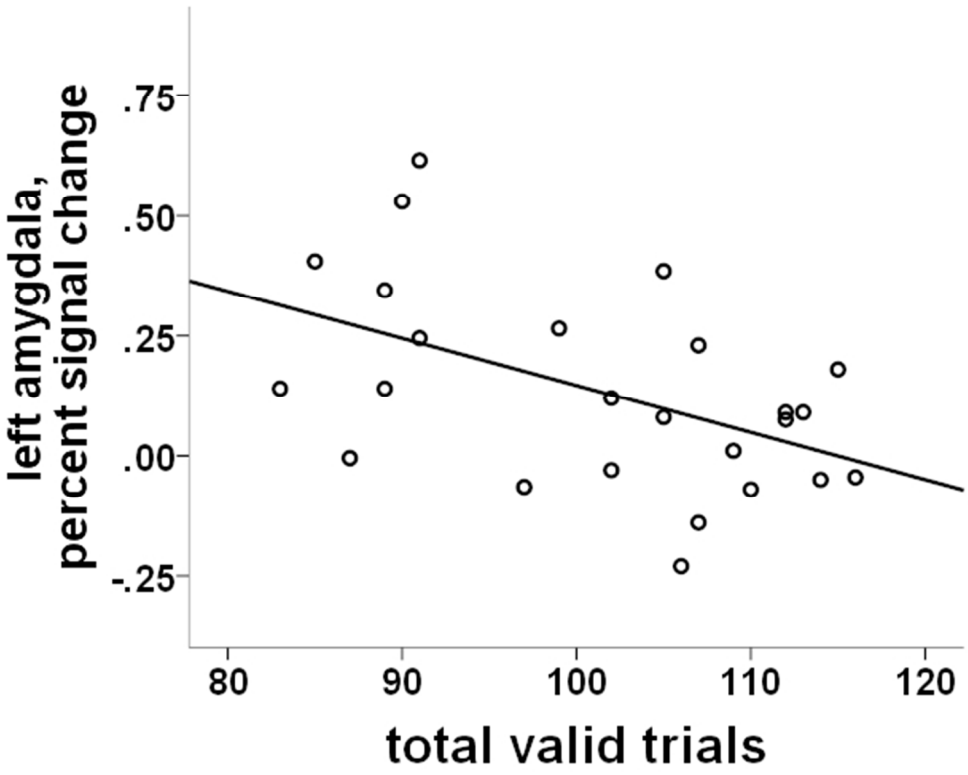

Figure 5: Scatterplot of the correlation (r = .5, p = .012) between valid trials and percent signal change for negative stimuli in the left amygdala ROI for the ADHD group.